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FACTORS INFLUENCING RENAL VASCULATURE DURING ANESTHESIA, TRAUMA, AND OLIGURIC RENAL FAILURE STATES IN MAN

FINAL REPORT

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Micropuncture studies performed in this laboratory revealed a reduction in both proximal tubular pressure and glomerular filtration rate in animal models of acute renal failure, making a vascular or glomerular mechanism the most attractive. Application of arteriography and xenon washout to assessing renal cortical perfusion in man revealed a global reduction in patients with acute renal failure sufficient to account for the failure of filtration and function. An identical hemodynamic and angiographic picture in patients (SEE REVERSE SIDE)

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20. ABSTRACT (continued)

in whom acute renal failure followed shock, hemolysis, sepsis, and a wide variety of pharmacologically and chemically unrelated nephrotoxins suggested an intrarenal final common pathway. Investigations in this laboratory revealed a striking influence of prior sodium intake on the pathogenesis of acute renal failure, raising the possibility that the renin-angiotensin system was involved. This led to an exploration of the role of angiotensin in the control of the normal renal circulation, where it plays a key role, and to a systematic exploration of angiotensin antagonists and their influence on the renal circulation. Because in models of acute renal failure the angiotensin antagonist led to a drop in blood pressure, major recent investigation was oriented toward developing agents with increased specificity for the kidney. Most recent investigation has involved the exploration of intraglomerular angiotensin receptors which appear to differ from those in the vasculature.

Summary

Our overall goal in the project has been to identify factors which predispose to and sustain acute renal failure following trauma or toxins in animal models and in man. Micropuncture studies in animal models of acute renal failure induced by glycerol (myohemoglobinuric) and bichloride mercury (nephrotoxic) revealed a fall in glomerular filtration rate as the major mechanism responsible for the failure of renal excretory function. This observation ruled out tubular disruption with passive backflow of filtrate as the major mechanism responsible for failure of renal excretory function. Because the glomerular membrane was morphologically normal, the failure of glomerular filtration rate could be attributed either to a vascular mechanism which reduced glomerular capillary pressure to a level too low to sustain filtration or to tubular obstruction with failure of filtration due to back pressure. Micropuncture of proximal tubules revealed a very low hydrostatic pressure in those tubules which were not collapsed. A low pressure, clearly, was not compatible with tubular obstruction, making a vascular mechanism the most attractive possibility.

At this time renal blood flow was known to be reduced to about one-third of normal in patients with acute renal failure. A logical dilemma was raised by the fact that blood flow was reduced to an equal degree in patients with chronic renal failure or congestive heart failure in whom renal function was abnormal but much better preserved than in patients with acute renal failure. Our application of xenon tracer studies and renal arteriography to the assessment of the renal vasculature in patients with acute renal failure resolved this dilemma. An equivalent reduction in renal blood flow in acute and chronic renal failure was associated with a strikingly different pattern of perfusion within the kidney. In patients with acute renal failure there was a global and uniform reduction in cortical blood flow to about one-third of normal--a reduction sufficiently large that no glomerulus would receive a sufficiently high blood flow to sustain filtration. In patients with chronic renal failure, conversely, an equivalent reduction in renal blood flow was associated with preservation of normal flow rates within regions of the renal cortex, easily identified by renal arteriography, which would be sufficient to maintain filtration rate in those regions.

These studies not only resolved the dilemma but raised interesting and potentially important pathogenetic possibilities. The observation that the arteriogram and renal perfusion pattern was identical in response to a wide variety of insults including trauma, shock, hemolysis, and a wide variety of chemically and pharmacologically unrelated nephrotoxins raise the interesting possibility that a final common pathway within the kidney was activated and was

responsible for the sustained reduction in renal perfusion and function.

Parallel studies in animal models in our laboratory have revealed that increased sodium intake was the most consistent maneuver for preventing acute renal failure and dehydration and restriction of sodium intake potentiated it. These maneuvers are known, respectively, to reduce and increase intrarenal and plasma renin activity. Angiotensin, the product of the renin-angiotensin system, is the most powerful renal vasoconstrictor agent yet identified. These observations, viewed in the light of the possibility of an intrarenal final common pathway raised by the clinical investigation, led to a detailed study of the renal response to angiotensin and, when they became available, to a detailed study of agents suitable for pharmacologic interruption of the renin-angiotensin system.

We showed that angiotensin would reduce renal blood flow in normal man with doses as low as 1 ng/minute--producing plasma concentrations well within the pnysiological range. The pattern of the renal response resembled that in acute renal failure. The observation that prolonged infusion of angiotensin would induce acute renal failure in rabbits provided further impetus to studies in this area.

The first antibody directed against angiotensin II was developed in our laboratory and preliminary studies indicated that effective immunization against angiotensin II would not prevent acute reanl failure in animal models. Parallel studies elsewhere indicated that antibody directed against renin would prevent acute renal failure, but the antibody was weak and large volumes had to be administered to the animal, and acute renal failure as a state which is sensitive to plasma and extracellular fluid volume. Because the antibodies are polar and large, the possibility that they did not gain effective entry to the receptors within the kidney had to be entertained.

At this time a series of agents which produce relatively specific pharmacologic interruption of the renin-angiotensin system became available. For obvious reasons major emphasis was given to assessing their impact on acute renal failure in animal models and their clinical pharmacology in man. We demonstrated that these agents would reverse the effects of restriction of sodium intake on the kidney, suggesting that the renal response to this modest reduction in extracellular fluid volume was sustained by angiotensin. In animal models we showed that both classes of agent would acutely reverse the reduction in renal perfusion but it was not possible to influence the course of acute renal failure. The major problem with these agents lay in the fact that angiotensin is responsible for maintaining total peripheral resistance and blood pressure through its systemic vascular actions in states in which volume is threatened. We have shown in patients in whom plasma volume is expanded that the renin-angiotensin

system is activated (in advanced congestive heart failure) but pharmacologic interruption of the renin-angiotensin system with a converting enzyme inhibitor will reverse the renal functional abnormality and induce a diuresis and natriuresis. These agents, however, could not be applied to reversing the renal effects of trauma and early acute renal failure because of the blood pressure problem.

Fortunately circumstantial evidence suggested tht the renal vascular angiotensin receptor differed sufficiently from systemic vascular angiotensin receptors that agents with greater specificity might be found. This work, which has involved us since the close of DA-49193-MD-2497, is still in progress.

Foreward

For the protection of human subjects we have adhered to policies of applicable Federal Law 45CFR46.

In conducting the research described in this report, we have adhered to the "Guide for Laboratory Animals Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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A. STUDIES IN NORMAL MAN

(A1) Studies in over 150 normal subjects have demonstrated that the disappearance of xenon from the normal human kidney after intra-arterial injection can be described, as in the dog, as a sum of four exponentials. Several lines of evidence (see sections A5, B1, B2, B5, B6, D1, D3) suggest strongly that the early rapid flow componment represents perfusion of the renal cortex in man, as it does in the dog. It has also been possible to show that a short curve demanding less than 5 minutes of recording time can approximate the rapid flow component defined by the usual analysis requiring 40 minutes of recording. In the short method the value of 3 minutes is used as an approximation of the two slowest components. This represents an advance because, particularly in the sick patient, it is frequently impossible to achieve the steady state for a prolonged period.

(A2) Angiography, which must be caried out with this method in order to define the renal artery for selective catheterization, has been shown to ve minimal effects on cortical perfusion. The only change induced by angiography is an increase in the disappearance of the third component which probably represents washout of isotope from the renal papilla by the osmotic diuresis.

(A3) Sodium restriction results in a characteristic change in intrarenal hemodynamics with a decrease in the flow rate and percentage of flow in the cortical component and a reciprocal increase in the second component flow rate and percentage, probably representing an increase in the perfusion of a juxtamedullary zone. Intravenous dextran failed to reverse the pattern, suggesting that the reduction in cortical perfusion was not a manifestation of the plasma volume reduction induced by sodium restriction. The renal hemodynamic pattern induced by sodium restriction is similar to that reported in the dog as the response to angiotensin and to direct stimulation to the sympathetic nerves, and is also similar to the pattern induced by a head-up tilt in man (see section C3).

(A4) Chlorothiazide had no effect on the intrarenal distribution of blood flow in subjects on a low salt diet. Ethacrynic acid induced a dramatic response, providing that diuretic-induced plasma volume production was prevented. The hemodynamic response to ethacrynic acid, which consisted primarily of a decrease in the flow rate and percentage of flow in the second flow component in a pattern similar to that induced by a high salt diet, provides corroborative evidence for the importance of hemodynamic changes in the kidney in sodium homeostasis.

(A5) Epinephrine injected into the renal artery results in a sharp reduction in cortical perfusion evidenced both by absence of the rapid flow component and failure of contrast

medium to reach the cortical vasculature. Recovery is complete within 3 minutes. The pattern of recovery from epinephrine characteristically shows the gradual appearance of an increasing percentage in the rapid flow component. This component has a normal flow rate from the time it becomes recognizable. The pattern of recovery suggests that areas within the kidney recover normal flow while others remain severely ischemic, typical of response of the kidney to a large number of stimuli. Neither the xenon washout nor the arteriogram showed evidence of a "shunt" mechanism of the type proposed by Trueta.

(A6) Phentolamine, the alpha adrenergic blocking agent, did not increase renal blood flow significantly when infused into the renal artery in doses up to 3 mg/min in subjects in balance on a low salt diet. Combined studies with phentolamine and epinephrine (see Section A5) showed that doses as low as 0.1 mg/min produce significant alpha blockage. These findings suggest that the reduction in renal blood flow induced by sodium restriction is not mediated by the sympathetic nervous system. In addition, this approach will be extremely valuable in defining the states in which sympathetic activity to the kidney plays a significant role in the vascular response.

(A7) Acetylcholine infused into the renal artery produces a dose related increase in renal perfusion, primarily of the renal cortex with a threshold dose of 1 microgram/min. Peak responses are achieved with 100 micrograms/min which is 1/400 the dose during intravenous infusion which produces a threshold systemic response. The agent is therefore extremely safe and shows great potential in the evaluation of active renal vasoconstriction. Atropine, 0.4 mg administered 1 to 4 hours before the acetylcholine infusion, resulted in a parallel shift in the dose-response curve, showing that the acetylcholine acted on muscarinic receptors. Caution must be excerised in the interpretation of the acetylcholine dose-response curve in settings in which atropine is included in the premedication.

(A8) Dopamine infused intravenously produces a dose-related increase in blood flow in doses from 1 microgram/Kg/min to 3 microgram/Kg/min. In this dose range dopamine has no effect on systemic blood pressure, heart rate or the electrocardiogram. An increase of the dose to 7 micrograms/Kg/min resulted in subjective symptoms, awareness of cardiac pulse, increase in pulse rate and increase in systolic pressure; all are manifestations of the alpha and beta stimulating effect of this agent. With an increase in dose the renal vascular response was reduced, suggesting that a prominant alpha constrictor effect of the agent had become dominant. Because of the great potential of this agent in the treatment of shock and oliguric states a clear demonstration of its specific pharmacodynamic properties in man is of extreme importance.

(A9) Angiotensin infused into the renal artery in man produces a decrease in perfusion similar to that induced by epinephrine. As in the dog, doses of angiotensin which reduce renal blood flow sharply do not have a prominant effect on the interlobar and arcuate arteries evaluated by selective arteriography. This provides an important line of evidence which suggests that angiotensin is not the only mediator in acute renal failure, because these vessels are extremely attenuated in patients with that syndrome.

B. INTRARENAL HEMODYNAMICS IN ACUTE OLIGURIC STATES

(B1) Our experience of the study of acute oliguric states in man extended to over 50 patients. In every case intrarenal hemodynamics have been characterized by the disappearance of the rapid flow component of xenon washout from the kidney, which probably represents a preferential reduction in cortical perfusion. The most frequently cited evidence in man that acute renal failure is not due to a hemodynamic abnormality with failure of glomerular filtration has been the fact that many patients with chronic renal failure have a similar reduction in mean blood flow, to approximately 1/3 of normal, with better-maintained renal function. These studies have shown that patients with chronic renal failure have a different pattern of intrarenal perfusion with the maintenance of small areas within the cortex which have a rapid flow component and presumably a flow rate adequate for the maintenance of glomerular filtration. These areas are also apparent in the selective arteriogram. In acute renal failure states it is possible to calculate that glomerular capillary pressure is reduced sifficiently as to preclude the possibility of continued filtration.

(B2) The interpretation of the xenon washout curve in patients with acute renal failure was corroborated by the characteristics of the renal arteriogram which shows failure of visualization of the cortical vessels, severe attenuation of the distal interlobar and arcuate vessels, delayed transit of contrast agent through the kidney and absence of the normal accentuated density of the cortical nephrogram. These changes are manifestations of active constriction of the cortical vessels, with a decrease in the normal preferentially high perfusion rate in the cortex. They provide no evidence of a shunt mechanism. The findings at open renal biopsy also supported this interpretation because the kidneys in these patients bled poorly on incision. The renal cortex of patients with cortical necrosis (see section B6) failed to bleed on incision. The arteriographic findings have more than pathophysiologic implications because several features in the arteriograms differ in patients with acute renal failure, allograft rejection, acute oliguric glomerulonephritis, the hepatorenaly syndrome and cortical necrosis. It thus appears that selective renal arteriography may become a valuable

adjunct in the differential diagnosis of selected patients in acute renal failure.

(B3) The wide variety of unrelated insults which induce a remarkably similar hemodynamic, arteriographic, histologic and functional picture suggests that a "final common pathway" intrinsic to the kidney capable of inducing and maintaining severe preglomerular vasoconstriction plays a central role in the pathogenesis of the syndrome. The inciting factors include shock, trauma, hemolysis, prolonged ischemia associated with transplantation, and the effects of a number of pharmacologically and chemically distinct nephrotoxins. Nephrotoxins studied to date include bichloride of mercury, carbon tetrachloride, a number of antibiotics including cephaloradine, sodium cholistimethate and kanamycin, and organic mercurials.

(B4) Catheters left in the renal artery at the time of transplantation in selected cadaveric allograft recipients (see section D4) have made it possible to carry out frequent sequential blood flow determinations. In six patients who suffered acute renal failure after transplantation it was noted that a rapid flow component reappeared 2 to 5 days before the onset of the early diuretic phase. Initially, the rapid flow component was small and evanascent, disappearing on some occasions. Diuresis became established when the rapid flow component became stable, being present on most determinations. This observation lends credance to the possibility that measures which will induce the reappearance and maintenance of a rapid flow component will prompt the kidney to resume its function.

(B5) It has been possible in two patients with oliguric renal failure after transplantation to study the transit of xenon through the kidney directly with the Anger scintillation camera. This instrument allows direct visualization of the isotope within the kidney during its transit. The normally functioning kidneys shows the rapid disappearance of isotope from the outer zone, one of the lines of evidence which supports the relationship between the rapid flow component and cortical perfusion. In both cases with acute oliguric renal failure, the rapid flow component was absent and the outer border of the kidney, the cortex, showed isotope clearance at the same rate as that in other parts of the kidney. It has therefore been possible to substantiate the earlier suggestion that the flow pattern in acute renal failure represents a preferential reduction in cortical perfusion.

(B6) Renal blood flow in patients with reversible acute oliguric renal failure has been consistently different from that in patients with renal cortical necrosis. In the latter, mean blood flow was considerably lower than that in acute renal failure and the monoexponential recognizable during early washout represented less than 50% the total flow, rather than

the typical 70 to 90% found in this component in patients with acute renal failure. This method along with selective arteriography therefore shows great potential in separating reversible and irreversible renal lesions. Because of the sampling problem inherent in renal biopsy this approach will be of great prognostic value if further experience corroborates this observation.

(B7) A pilot study on the effects of acetylcholine infusion in two patients with acute oliguric renal failure was carried out. In order to assess the acute effects and insure that the agent did no harm, a brief infusion lasting approximately 30 minutes was carried out. In one patient the vasodilator induced the reappearance of a rapid flow component and unequivocal evidence of improved cortical infusion in the selective arteriogram. This patient went on to recover. In the other patient the acetylcholine administered in doses of up to 900 micrograms/minute failied to improve renal perfusion. In this patient histologic examination of the kidney revealed diffuse intravascular thrombosis in the small intrarenal vessels due to hyperaute rejection. A vasodilator cannot be expected to act at a stage in which occlusion of vessels plays a central role. The pilot study on the first patient suggests that acetylcholine will dilate the constricted vessels in patients with acute renal failure. A more prolonged duration of infusion may be required to reestablish renal function.

(B8) Patients with the hepatorenal syndrome show a characteristic renal hemodynamic and angiographic pattern which includes an extremely abnormal blood flow to the kidney, an extremely unstable disappearance of xenon from the kidney consistent with active phasic vasoconstriction and a selective arteriogram which shows even more attenuation of the proximal interlobar and second order intrarenal vessels than is present in patients with acute renal failure. Beading of the larger arteries in some patients was extreme, resembling polyarteritis nodosa. Postmortem injection of the renal vessels in these patients have shown changes were due to active vasoconstriction. Phentolamine did not reverse the process suggesting that the sympathetic nerves were not involved.

C. STUDIES IN THE PATIENT WITH HYPERTENSION

(C1) the pattern of intrarenal blood flow distribution was determined in over 150 patients with essential hypertension. Those without small vessel disease apparent in the selective arteriogram, and with normal renal function appeared to have a normal perfusion pattern, but it has been possible to identify two abnormalities of renal perfusion in this population (see sections C4 and C5). In patients with a normal selective arteriogram, renal perfusion was rarely below the lower limit of normal. In patients with severe abnormalities of the intrarenal vessels due to nephrosclerosis, flow was always reduced, primarily due to a decrease in cortical perfusion. A

good correlation was found between the degree of abnormality in cortical perfusion and renal function in this population. In patients with intermediate degrees of vessel abnormalities in the arteriogram the relationship to blooe flow was variable, approximately one half of patients with a moderate to severe abnormality showing abnormalities of perfusion. It is therefore clear that the selective arteriogram in this intermediate group cannot be used to assess renal perfusion and that an ancillary method which measures blood flow directly must be available. Patients with a moderate to severe abnormality in the selective arteriogram were characteristically older, had a more prolonged duration of hykpertension, had higher admission blood pressures, a significant reduction in renal function and more evidence of other side effects of hypertension including retinopathy and left ventricular hypertrophy. It seems likely on this basis that the vascular changes seen in this population represent the effects of prolonged and severe hypertension. The possibility is raised that the vascular changes which have occurred secondary to hypertension at this stage played a role in potentiating the process (see section C2).

(C2) It was possible to calculate the rate of renin secretion from the kidney to patients with hypertension as the product of renal blood flow and the arteriovenous difference in renin content. Young patients with essential hypertension, normal renal function, normal blood flow and no evidence of small vessel disease in the selective arteriogram have minimal rates of renin secretion, probably not different from that in normal man. Patients with significant renal artery stenosis or with accelerated hypertension had highly significant increases in the rate of renin secretion. Patients described in section C1 with moderate small vessel disease in the selective arteriogram and a small decrease in renal function also had a significant increase in the rate of renin secretion.

(C3) The effects of a 60° head-up tilt were assessed in five patients with essential hypertension. The characteristic response with a reduction in mean blood flow, flow rate and the percentage of flow in the rapid flow component, a pattern similar to that induced by salt restriction in man and direct sympathetic nerve stimulation in the experimental animal. In association with the decrease in cortical perfusion, there was a sharp and significant increase in the rate of renin secretion from the kidneys studied, apparent within five minutes. It seems likely that the vascular effects and the increased renin secretion were induced by sympathetic activity to the kidney.

(C4) Essential hypertensives under the age of 30 years have a renal blood flow rate significantly greater than that in normal subjects in the same age range. The increase in perfusion is not related to the arterial pressure at the time of study, or the use of antihypertensive agents. It was possible to demonstrate that approximately one half ot hese

subjects failed to show the characteristic renal vascular response to salt restriction (see section A3). The flow values and intrarenal blood flow distribution in these subjects is similar to that in normal man on a high salt intake. The essential hypertensives had a similar net negative sodium balance and weight loss in response to salt restriction and were able to reduce their urine sodium concentration to minimal levels. If intrarenal hemodynamics is important in renal sodium homeostasis it seems likely that these patients use different mechanisms for achieving salt balance.

(C5) The series of xenon washout curves were analyzed independently by two individuals in order to provide an index for assessing differences between curves which can be attributed to analytic error. Larger differences probably reflected a real difference in renal perfusion. With the confidence interval on curve analysis it was possible to show that in normal subjects sequential studies on the same or the contralateral kidney showed differences larger than predicted on the basis of curve analysis, probably reflecting small phasic changes in renal blood flow. In patients with essential hypertensin both the magnitude and prevalence of the changes was considerably greater than normal. This disparity in blood flow to the two kidneys in patients with essential hypertension has been noted earlier, and attributed to differences in the rate of progression of small vessel disease in the two kidneys. In view of the present findings that sequential studies in the same kidney show the same variability it is difficult to attribute this to an organic lesion. Some functional influence, perhaps the sympathetic nervous system, seems to produce flow instability in the patient with essential hypertension. The presence of this phenomenon was not related to the patients' age, sex, the history of their hypertension and its therapy, renal function, state of sodium balance or any discernible clinical manifestation. The only subject (see section A6) to show an increase in blood flow during phentolamine infusion was an essential hypertensive. The possibility that sympathetic activity to the kidney occurs in some patients of essential hypertension and not in normal subjects must be assessed.

(C6) The use of vasodilators to differentiate organic from functional renal vascular abnormalities in patients with essential hypertension was performed. In some patients there was a decrease in the blood flow response to acetylcholine or dopamine, along with a fixed angiographic lesion; a constellation of findings which suggests the presence of organic, fixed vascular lesions in these patients. In two thirds of patients, the blood flow increase in response to dilators was considerably larger than normal and the arteriogram became normal during acetylcholine infusion, suggesting the presence of a functional abnormality, active vasoconstriction of the vessels.

(C7) Patients with renal artery stenosis of sufficient severity to produce a renal hemodynamic abnormality with a reduction in blood flow appear to have a different intrarenal flow pattern from patients with renal parenchymal disease or nephrosclerosis. In the latter the characteristic vascular pattern included a reduction in the percentage of flow in the rapid flow component but with a relatively normal flow rate in that component, similar to the pattern of recovery from epinephrine (see section A5). Patients with renal artery stenosis show a relatively normal distribution of blood flow within the kidney but a decrease in the rate constant of flow rates within the various intrarenal compartments. It has been possible to demonstrate the same pattern in dogs with partial renal artery stenosis. If this observation can be corroborated with further studies this approach shows promise in differentiating a significant renal artery stenosis from small vessel disease distal to the stenosis in the same kidney.

(C8) Patients with pyelonephritis have shown a reduction in renal blood flow primarily due to the reduction in the cortical component of flow, out of proportion to the abnormalities of the distal interlobar and arcuate arteries visualized in the selective arteriogram. If the abnormality in this vascular order represents the effects of hypertension (see section C1) it seems likely that the vascular abnormalities which in the cortex of the patient with pyelonephritis are not due to hypertension, as suggested by ome investigators. This observation would favor the suggestion of other investigators that abnormalities of renal perfusion in the patient with pyelonephritis contribute to the progression of hypertension, rather than being its sequal.

D. RENAL HEMODYMAMICS IN THE TRANSPLANTED KIDNEY

(D1) Studies in over sixty patients with transplanted kidneys showed a close correlation between glomerular filtration rate and the percentage of flow in the rapid flow component. In this situation all of the glomerular filtrate is coming from the kidney studied. This observation suggests strongly that xenon washout can be used to assess the functional status of the kidney in situations in which glomerular filtration cannot be measured because of urinary losses, oliguria or where GFR is changing acutely. The relationship also provides one of the lines of evidence (see section A1) that the rapid flow component represents cortical perfusion.

(D2) Serial studies carried out with catheters placed in the renal artery at the time of transplantation have show that changes in the rapid flow component represent one of the earliest manifestations of acute allograft rejection. This observation should make it possible to institute appropriate therapy earlier during acute rejection than has been possible heretofor, perhaps improving the overall results.

Intra-arterial therapy (see section C4) may also provide an increased therapeutic ratio in the treatment of allograft rejection.

(D3) An excellent correlation was found between biopsy evidence of vascular abnormalities in the renal cortex of patients with chronic renal allograft rejection (assessed by Dr. G. Dammin) and the characteristics of the rapid flow component. Considerably less pathology was necessary to produce a significant hemodynamic defect at the level of the afferent arteriole than at the level of the interlobular arteries. It was also possible to identify several patients in whom a severe phasic abnormality of perfusion was present despite relatively normal vessels suggested strongly that a functional vascular abnormality contributed to the abnormalities of perfusion. A similar abnormality of perfusion is found during early allograft rejection when the vessels are patent and free of local abnormalities, except for a perivascular infiltrate of mononuclear cells. The mediators of this hemodynamic abnormality and its relationship to the natural history of allograft rejection remains to be determined.

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